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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,036	09/30/2002	Paul R. Sanberg	LAY-014PCTUS	5509

51951 7590 12/29/2005

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EXAMINER
BALLARD, KIMBERLY A

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,036	SANBERG ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/15/02, 4/14/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Invention I, claims 1-4 and 7-12 [*sic*], in the reply filed on December 5, 2005 is acknowledged. It is noted that in applicant's response to the restriction requirement applicant has denoted Group I as "claims 1-4 and 7-12 [*sic*]" whereas the previous office action (restriction requirement dated November 4, 2005) listed Group I as "claims 1-4 and 7-17." The examiner assumes this was an unintentional typographical error on the part of applicant and therefore concludes that Invention I includes claims 13-17. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The applicant has canceled claims 5-6; claims **1-4** and **7-17** are pending and under examination in the current office action.

Information Disclosure Statement

Signed and initialed copies of the IDS forms submitted November 15, 2002 and April 15, 2003 are enclosed in this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the foreign application for patent or inventor's certificate on which priority is claimed pursuant to 37 CFR 1.55, and any foreign application having a filing date before that of the application on which priority is claimed, by specifying the application number, country, day, month and **year** of its filing. Specifically, the date is incomplete.

Claim Objections

Claim 15 is objected to because of the following informalities: the word "to" is missing, rendering the sentence grammatically incorrect. A "to" should be inserted as: "a sufficient number of neuronal cells or neural stem cells to a location..." Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 7-12, 14-15, and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Simm (BerlinOnline, March 3, 1999, as listed on applicant's IDS filed 11/15/02). The claims are drawn to methods of treating stroke in a patient who has undergone a stroke at least 3 months earlier, said method comprising delivering at least 2 million viable neuronal cells to at least one brain area involved in the stroke, wherein

the cells are selected from hNT neuronal cells, neural stem cells, HCN-1 cells, fetal pig cells, neural crest cells or a combination thereof. The claims are further drawn to a method of improving speech, motor performance, and sensory function in a person who has experienced brain damage which interferes with those functions, or a method of replacing nerves in an individual CNS lost to neurodegenerative disease, trauma, ischemia or poisoning, comprising administering a sufficient number of neuronal cells into the damaged area.

Simm teaches that patients who had suffered a stroke half a year to six years previously were each injected with about two million hNT neurons (a human neuronal cell) in the damaged region of the brain. Several months after the procedure, patients reported improvement in being able to walk, move and speak. Because the ability to walk is governed not only by the motor cortex but also by sensory feedback, such as balance and visual input (see Kandel et al., Principles of Neural Science, McGraw-Hill, 2000, p. 747), the improvement observed in walking would also emcompass improvements in sensory functions, thus meeting limitations of claims 14 and 15. Moreover, it would be an inherent property of the injected neurons to migrate to damaged areas, as noted for example in Synder and Macklis (*Clin. Neurosci.* 1996, 3: 310-316, see especially pp. 313-314 under hypoxic-ischemic brain injury). Synder and Macklis explain that donor-derived stem cells transplanted into brains of mice subjected to hypoxic-ischemic damage preferentially migrate and integrate extensively within the large ischemic (i.e. damaged) areas that typically span the length of the injured hemisphere. Therefore the limitation of claim 15, reciting the injection of neuronal cells

[to] a location from which the neuronal cells migrate to the damaged area, and the limitation of claim 17, reciting a method of replacing nerves, would both be met.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Canadian Patent Application CA 2213780 by Gloster and Miller, filed 22 August 1997, published 26 February 1998. The claim is drawn to a method of replacing nerves in an individual central nervous system (CNS) that were lost to neurodegenerative disease, trauma, ischemia or poisoning, comprising administering to the individual a sterile composition of a sufficient number of neuronal cells.

The Canadian patent application teaches implanting neurons, astrocytes or oligodendrocytes into the CNS, PNS, spinal cord or other tissue of a human who is suffering from a neurodegenerative disease or neurotrauma (see claims 14-19). The patent application also discloses pharmaceutical compositions for use in implant therapy which include precursor cells or neurons, astrocytes or oligodendrocytes differentiated from the precursor cells (p. 9, lines 12-16). It would be an expected property of the compositions to be sterile if they are intended for human therapeutic use.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,851,832 (Weiss et al., issued 12/22/98, filed 6/7/95, as listed on applicant's IDS filed 11/15/02) in view of Sanberg et al. (Soc. Neurosci, Abstr. 140.9, 1997, 23 (1-2): 346 and in further view of Grabowski et al. (*Exp Neurol.* 1994, 127(1): 126-136, abstract only).

The claims are drawn to methods of treating stroke in a patient who has undergone a stroke at least 3 months (or 3 hours) earlier, said method comprising delivering at least 2 million viable neuronal cells to at least one brain area involved in the stroke, wherein the cells are selected from hNT neuronal cells, neural stem cells, HCN-1 cells, fetal pig cells, neural crest cells or a combination thereof.

The '832 patent discloses a method for the treatment of neurodegenerative diseases comprising administering to a mammal neural stem cell progeny that have been induced to differentiate into neurons and/or glia (column 11, lines 13-17). CNS disorders in the '832 patent encompass numerous afflictions such as neurodegenerative diseases (e.g. Alzheimer's and Parkinson's), acute brain injury (e.g. stroke, head injury, cerebral palsy), and a large number of CNS dysfunctions (e.g. depression, epilepsy, and schizophrenia) (column 3, line 7-12). The patent teaches that acute brain injuries (such as stroke) often result in the loss of neural cells, leading to inappropriate functioning of the affected brain region (column 3, lines 22-24). As disclosed by the '832 patent, treatment of neurodegenerative disease using progeny of human neural stem cells involves first having the patient undergo a CT scan to determine the coordinates of the region to receive the transplant, then using injection cannula to inject

the tissue suspension to the correct coordinates (column 42, example 14). And in an animal model of stroke precipitated by occlusion of the carotid arteries, the '832 patent discloses that neural stem cells are implanted in the lesioned areas. Also, in the actual transplantation procedure, it is taught that burr holes are drilled in the skull to allow access for cannula and injection syringes (column 62, lines 33-35), thus meeting a limitation of claim 2.

The '832 patent teaches that live neural stem cells prepared for transplantation are resuspended to a cell density of $1.5x10^6$ cells/ml (column 62, lines 16-22), and 1-3 μl are administered in an animal model for transplantation (column 62, lines 38-40), which would be approximately 1500-4500 cells. However, the '832 patent is silent as to the timing of the administration of neuronal cells in relation to the stroke.

Sanberg et al. teach that transplantation of hNT cells to ischemic rats produces dose-dependent behavioral recovery. Adult rats subjected to ischemic embolism by middle cerebral artery occlusion (MCAo, an art-accepted animal model of ischemic stroke) were allowed to recover for one month before transplantation surgery. Animals were transplanted with 0, 5,000, 10,000, 20,000 and 40,000 hNT cells. One month following transplantation, Sanberg and colleagues observed that animals that had received 40,000 hNT cells showed significant behavioral recovery that persisted up to 3 months, and showed more significant recovery than the other transplant groups. Thus, the greater the number of cells transplanted following ischemic injury, the greater the degree of functional recovery.

Grabowski et al. teach another model of transplantation in which fetal cortex is grafted into the infarcted cortex of rats that having undergone middle cerebral artery occlusion 5-7 days, 3 weeks, or 8 weeks prior. Grabowski teaches that when transplantation surgery is delayed, graft survival is significantly improved. These investigators conclude that a delay between lesion and transplantation is desirable in this stroke model. Thus waiting at least 3 months (as stated in the instant claims) before administration of therapy would seem reasonable based on the findings of Grabowski et al.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of treating neurodegenerative disease taught by the '832 patent by administering a larger number of neuronal cells, as taught by Sanberg et al., after a period of at least 3 months, as taught by Grabowski et al. One of ordinary skill in the art would be motivated to do so because Sanberg et al. teaches a dose-dependent behavioral recovery in ischemic rats when transplanting greater numbers of hNT cells. The human brain is reported to have approximately 100 billion neurons, and one of ordinary skill in the art would estimate that the rat brain would have far fewer neurons due to its being proportionately smaller (when body size is adjusted for) and because the rat brain has far less surface area (indicated by the lack of convolutions on brain surface). If ischemic damage of equal intensity were to occur in comparably-sized brain regions in a rat and a human (again, adjusted for body size), it would be reasonable to predict that the number of neurons affected in the human would exceed the number of affected neurons in the rat. Therefore, it is also reasonable to

contemplate using a greater number of neuronal cells to treat damage caused by a stroke in a human than to treat damage caused by ischemia in a rat. And one of ordinary skill in the art would be motivated to treat stroke patients after a longer period following stroke occurrence because Grabowski teaches that greater survival of transplanted neural tissue is observed with a longer delay between ischemic damage and transplantation. The artisan would thus expect that transplanted neuronal stem cells could be successfully used to treat stroke patients because transplanted hNT neuronal cells had already shown promising results in the behavioral recovery of ischemic rats.

Claims 7-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanberg and Borlongan (Soc. Neurosci, Abstr. 232.9, 1996, 22 (1-3): 578) in view of U.S. Patent No. 5,851,832 (Weiss et al., issued 12/22/98, filed 6/7/95, as listed on applicant's IDS filed 11/15/02) in further view of Uchida et al. (*Exp Neurol*, 1995, 132: 194-208).

The claims are drawn to a method of improving speech, motor performance, cognition, and sensory function in a person who has experienced brain damage which interferes with those functions, wherein the brain damage is due to stroke and wherein the method comprises injecting a sterile composition of a sufficient number of human neuronal cells or human stem cells into the damaged area or to a location, such as the cisternae, from which the neuronal cells migrate to the damaged area. The claims are further drawn to a method of replacing nerves lost to neurodegenerative disease,

trauma, ischemia or poisoning in an individual CNS, comprising administering a sterile composition of a sufficient number of neuronal cells into the damaged area.

Sanberg and Borlongan teach that transplantation of human teratocarcinoma neuronal cells (hNT) to ischemic rats produces recovery of motor function and passive avoidance behavior. Adult rats were subjected to ischemic embolism by middle cerebral artery occlusion (MCAo, an art-accepted animal model of ischemic stroke) were allowed to recover for one month before being tested for asymmetric motor behavior (elevated body swing task, EBST) and passive avoidance behavior (a cognitive test for learning and memory). Animals received transplants of either hNT cells, or fetal striatal or cerebellar cells and again allowed to recover before being evaluated at 1, 2, and 3 months post-transplant. Sanberg and Borlongan report that one month following transplantation surgery, significant recovery in both the EBST and passive avoidance tasks was observed in groups that received hNT cells or fetal striatal tissue. Control animals were reported to show no behavioral recovery. Sanberg and Borlongan thus conclude that transplantation of hNT cells into the infarcted striatum of rats having transient focal ischemia improves motor and cognitive deficits associated with such ischemia, thus meeting limitations of claims 10-12 and 13 of the instant application. The elevated body swing task (EBST) used to assess recovery in the Sanberg and Borlongan reference is considered a sensorimotor test (see, for example, Roof et al., *Stroke*, 2001, 32(11): 2648-2657, particularly p. 2649). Therefore, one of ordinary skill in the art would come to the conclusion that both motor and sensory performance is improved with the transplant treatment *supra* as indicated by recovery in

the EBST, thus meeting a limitation of the instant claim 14. Because speech is specialized to humans, there is no appropriate animal model to evaluate recovery of speech function. However, it should be noted that speech can be affected by any number of brain regions damaged by a stroke. Accordingly, the ability to speak involves not only cognitive functioning, but also proper motor (e.g. tongue, lips, throat) and sensory (e.g. hearing, positional feedback from the tongue and lips) functioning. Thus, although speech recovery cannot be assessed in treating a rat model of stroke, recovery of cognitive, motor, and sensory functions in rats could be used to indicate an effective means of treating speech affected by stroke in humans. As mentioned *supra*, the occurrence of a stroke would be expected to affect any individual or combination of motor, speech, cognitive, or sensory performance depending on the brain region that is damaged (see for example Kandel et al., Principles of Neural Science, McGraw-Hill, 2000, pp. 1306-1316, which reports the types of damage that occur when different areas experience cerebral or spinal infarction). Therefore, in the process of treating an expansively damaged brain region, several functions (such as motor skills, speaking, cognition, and sensation) would reasonably be predicted to be affected by the treatment procedure, as evidenced by the Sanberg and Borlongan reference which shows improvement of sensorimotor and cognitive deficits in rats subjected to ischemia and neuronal transplantation.

The Sanberg and Borlongan reference is, however, silent as to the treatment's administration in humans as well as the migration of injected neuronal cells. The '832 patent discloses a method for the treatment of neurodegenerative diseases comprising

administering to a mammal (such as a human) neural stem cell progeny (which may also be derived from humans) that have been induced to differentiate into neurons and/or glia (column 11, lines 13-17). CNS disorders in the '832 patent encompass numerous afflictions such as neurodegenerative diseases (e.g. Alzheimer's, Parkinson's, Huntington's chorea, ALS), acute brain injury (e.g. stroke, head injury, cerebral palsy), and a large number of CNS dysfunctions (e.g. depression, epilepsy, and schizophrenia) and human demyelinating diseases (e.g. MS) (column 3-4). The patent teaches that acute brain injuries (such as stroke) often result in the loss of neural cells, leading to inappropriate functioning of the affected brain region (column 3, lines 22-24). As disclosed by the '832 patent, treatment of neurodegenerative disease using progeny of human neural stem cells involves first having the patient undergo a CT scan to determine the coordinates of the region to receive the transplant, then using injection cannula to inject the tissue suspension to the correct coordinates (column 42, example 14). It would be an expected property of the injected cell compostion to be sterile if it was used therapeutically in humans.

Uchida et al. teach that transplanted neuronal cells survive greater than one year in an adult host and these cells migrate some distance away from the implantation location. In this study, adult mice were injected in the striatum or lateral ventricle with neural plate tissue implants from transgenic heterozygous embryos expressing β-galactosidase (to identify donor cells). Uchida found that not only did donor cells survive in their adult hosts as much as one year following implantation, but also that many β-gal-positive cells migrated as much as 230 μm away from the main graft mass

in both striatal and intraventicular implantations, thus meeting a limitation of claim 15 of the instant application. Though these cells were injected into the lateral ventricle, one of ordinary skill in the art would know that the ventricles are interconnected to each other and to the cisternae, such that injection of a substance in one ventricle circulates to the other ventricular spaces, which would address the limitation of claim 16 of the instant application.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering human neuronal cells to treat ischemic brain damage in a rat model of stroke taught by Sanberg and Borlongan by treating stroke patients instead as taught by US Patent '832, and to administer these cells intraventricularly as taught by Uchida et al. One of ordinary skill in the art would be motivated to do so because Sanberg and Borlongan teach that sensorimotor and cognitive functions are improved following administration of hNT cells to the damaged area in ischemic rats and that a need for such treatment exists in humans who have suffered the debilitating effects a stroke, as indicated in the '832 patent. The artisan would have been further motivated to inject the cells cisternally, not only because Uchida teaches that implanted neuronal cells can migrate some distance from their implantation site, but also because the an intracisternal injection can be performed without drilling into the skull and is presumably less invasive (thus fewer potential complications). The artisan would thus expect that transplanted human neuronal cells could be successfully used to treat stroke patients because transplanted hNT neuronal

cells had already shown promising functional recovery in an animal model of stroke: transient focal ischemia in rats.

Conclusion

Claims 1-4 and 7-17 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kimberly Ballard
Art Unit 1649
December 16, 2005

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER